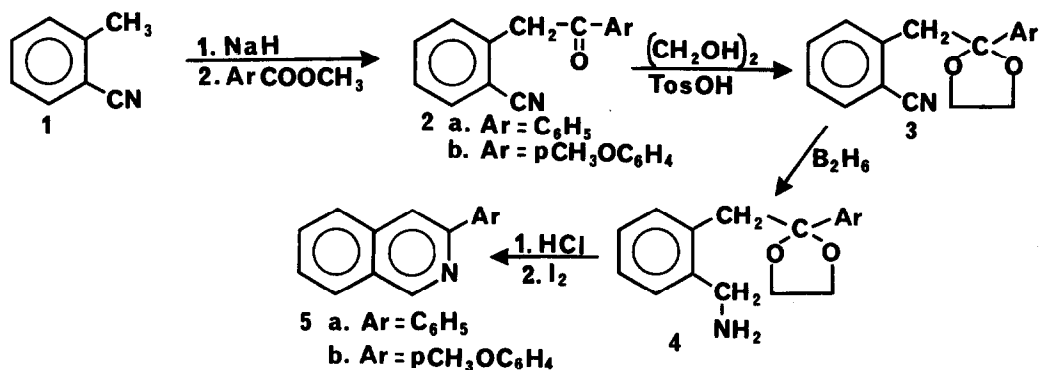


A NEW ISOQUINOLINE SYNTHESIS VIA ORTHO-SUBSTITUTED BENZYLAMINES

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The observation by Hauser et al ^{2,3} that the carbanion derived from *o*-tolunitrile 1 could be acylated with methyl benzoate to afford 2-benzoylmethylbenzonitrile 2a suggested the possibility of a simple synthetic route to 3-substituted isoquinolines. In our hands the benzoyl-



lation of the nitrile could be carried out in 54% yield using sodium hydride³ as a catalyst.

The benzoyl derivative (2a) was converted to the 1,3-dioxalane derivative 3a (mp 103°) in 95% yield. Reduction of 3a with diborane in tetrahydrofuran afforded the benzylamine 4a, isolated in 67% yield as the hydrochloride, mp 189.5-190.5 dec. Hydrolysis and cyclization were effected by refluxing 4a for 10 min. in aqueous methanol containing a small quantity of hydrochloric acid. The resulting solution was concentrated, made basic and extracted with chloroform and the dihydroisoquinoline derivatives dehydrogenated by addition of iodine at room temperature affording 3-phenylisoquinoline (5a), mp 99-102°, in 70% yield. The analytical sample melted at 102.5-103.5° (lit.⁴ 103-105°) and the overall yield from *o*-tolunitrile was 24%.

Repetition of the synthesis using methyl p-methoxybenzoate gave the following results: ketone 2b mp 96-97°, yield 40.6%; ketal 3b mp 127.5-128.5°, 86%; amine 4b (not isolated but cyclized directly), isoquinoline 5b isolated as the picrate (mp dec 243°) in 41% yield; and converted to the free base mp 100.5-101.5° (lit.⁵ 95°) in 86% yield. All of the compounds described have been characterized spectroscopically and have given satisfactory elemental analyses.

Work to extend this synthesis to the preparation of 1- and 4- substituted isoquinolines is now in progress. This work was supported in part by Public Health Service Grant No. HL 02170 of the National Heart and Lung Institute of the National Institutes of Health.

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